General

Guideline Title

Lenalidomide in multiple myeloma.

Bibliographic Source(s)

Chen C, Baldassarre F, Kanjeekal S, Herst J, Hicks L, Cheung M, Hematology Disease Site Group. Lenalidomide in multiple myeloma. Toronto (ON): Cancer Care Ontario (CCO); 2012 May 30. Various p. (Evidence-based series; no. 6-5). [86 references]

Guideline Status

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

Recommendations

Major Recommendations

Previously Untreated Multiple Myeloma

Previously Untreated Smoldering Multiple Myeloma

In asymptomatic patients with no evidence of myeloma-related hypercalcemia, renal dysfunction, anemia, or bone disease (smoldering multiple myeloma), the routine use of lenalidomide alone or in combination cannot be recommended.

Previously Untreated Symptomatic Multiple Myeloma

a. Single-agent lenalidomide: lenalidomide alone for first-line therapy in myeloma cannot be recommended for standard use in patients with previously untreated multiple myeloma.
b. Lenalidomide and dexamethasone: the combination of lenalidomide and dexamethasone is an acceptable first-line treatment option in patients of any age. The recommended dose of lenalidomide is 25 mg/day on days 1-28 every 35-day cycle for the first three cycles, followed by 25 mg/day on days 1-21 every 28-day cycle thereafter. A reasonable alternative is to proceed directly to the 28-day cycle dosing from the start if preferred. The use of low-dose dexamethasone, 40 mg/day on days 1, 8, 15 and 22 of a 28-day cycle, is preferred for safety; however, some patients with acute myeloma complications such as acute renal dysfunction, hypercalcemia, or hyperviscosity syndrome may benefit from high-dose dexamethasone (i.e., 40 mg/day on days 1-4, 9-12, and 17-20 of a 28-day cycle).

c. Other lenalidomide combinations: The combination of lenalidomide with other drugs is not recommended in this setting.

Relapsed or Refractory Multiple Myeloma

a. Single-agent lenalidomide: Lenalidomide alone for first-line therapy in myeloma cannot be recommended for standard use for patients with relapsed/refractory multiple myeloma
b. Lenalidomide and dexamethasone: Lenalidomide plus dexamethasone is recommended for myeloma patients who have received at least one prior line of therapy. The recommended dose is lenalidomide 25 mg/day on days 1-21 plus dexamethasone, either low-dose 40 mg/day on days 1,8,15, and 22 or high-dose at 40 mg/day on days 1-4, 9-12, and 17-20, with either being given on a 28-day cycle.
c. Other lenalidomide combinations: The combination of lenalidomide with other drugs is not recommended in this setting.

Subgroups of Patients Most Likely to Benefit From Treatment With Lenalidomide

a. For patients with newly diagnosed multiple myeloma, there is insufficient evidence to recommend lenalidomide in specific subgroups of patients. When lenalidomide is combined with dexamethasone, the use of low-dose versus high-dose dexamethasone may be preferable from a safety perspective, regardless of age.
b. For patients with relapsed/refractory multiple myeloma, lenalidomide plus dexamethasone is a reasonable treatment option for the following patient subgroups:
    i. Patients with at least one prior line of therapy: those patients who are less heavily treated (only one prior line of therapy vs. two or more) appear to benefit the most.
    ii. Patients who have received prior thalidomide or autologous stem cell transplantation (ASCT).
    iii. Younger or older patients: Advanced age should not be an absolute contraindication for the use of lenalidomide, as long as any adverse events are carefully monitored.
    iv. Patients with mild-to-moderate renal failure (creatinine clearance ≥30 mL/min and ≤60 mL/min): For patients with severe renal failure (creatinine clearance <30 mL/min), the Hematology Disease Site Group (DSG) cautions against the use of lenalidomide until additional evidence for its use in this subgroup becomes available.
    v. Patients with Immunoglobulin A (IgA) subtype, pre-existing peripheral neuropathy, and different levels of Eastern Cooperative Oncology Group (ECOG) performance status.
c. For patients with relapsed/refractory multiple myeloma, the following treatment guidelines for lenalidomide and dexamethasone may be considered:
    i. Full-dose lenalidomide may be initiated (25 mg/day dose), but it is reasonable to consider dose reductions for use beyond 12 months.
    ii. A longer period of lenalidomide use, if possible until progression, is a reasonable target.
    iii. Dexamethasone dose reductions may be used as needed for improved tolerability.

Lenalidomide Maintenance or Consolidation

a. Non-transplant patients: In non-transplant patients with multiple myeloma, there is insufficient evidence to support the use of lenalidomide maintenance or consolidation treatment following initial therapy.
b. Transplant patients: In the absence of a final full publication of supporting trials in the post-transplant setting (currently in the form of conference abstracts), the Hematology Disease Site Group suggests that lenalidomide maintenance at 10-15 mg/day continuously until progression is a reasonable option. Upon publication of the final analyses of supporting studies, providing the strength and direction of results remain unchanged from currently available abstract publications, lenalidomide maintenance at 10-15 mg/day continuously until progression is recommended.

Management of Toxicity

a. Venous thromboembolism (VTE)
   For newly diagnosed patients, and for relapsed and refractory patients who are not at high risk for bleeding or VTE, either low-dose aspirin (ASA) given orally at 100 mg/day or enoxaparin (low molecular weight heparin or LMWH) at 40 mg/day given subcutaneously can be used in patients treated with lenalidomide-based therapy to prevent thromboembolic side effects. For patients at high risk of VTE or bleeding, there is insufficient evidence to support a specific thromboprophylactic approach.

b. Cytopenias
   Insufficient evidence is available to recommend a uniform approach for the management of cytopenias. Lenalidomide dose reductions can be considered for patients who have responded clinically and biochemically to the full dose of lenalidomide. For those who require the full dose of lenalidomide for efficacy, the use of granulocyte-colony stimulating factor (GCSF) support can be considered for neutropenia.

c. Second Primary Malignancies (SPM)

Insufficient evidence is available to date to confirm or refute the association of SPM with lenalidomide use or to identify specific subgroups of patients at risk of SPM when treated with lenalidomide.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Multiple myeloma

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Hematology

Oncology

Intended Users

Advanced Practice Nurses

Nurses

Physicians

Guideline Objective(s)

To provide recommendations for the use of lenalidomide alone or in combination with other agents in patients with previously untreated or relapsed/refractory multiple myeloma

Target Population

Adult patients with previously untreated, relapsed, or refractory multiple myeloma

Interventions and Practices Considered

1. Lenalidomide
    - Single agent
    - Combined with dexamethasone
    - Maintenance therapy
2. Management of toxicities
    - Aspirin or enoxaparin (for venous thromboembolism)

Note: Lenalidomide was considered but not recommended in patients with asymptomatic previously untreated smoldering multiple myeloma.

Major Outcomes Considered

- Overall survival
- Progression-free survival (PFS)
- Time to progression (TTP)
- Response rate
- Incidence of serious toxicity

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search Strategy

The literature was systematically searched using the electronic databases MEDLINE (Ovid, 2000 to February 15, 1012), EMBASE (Ovid, 2000 to 2012 Week 7), and the Cochrane Library (Central Register of Controlled Trials, Database of Systematic Reviews and Database of Abstracts of Effects, 2000 to February 15, 2012). The search strategies used for the MEDLINE and EMBASE databases are shown in Appendix 2 in the original guideline document. This search has been adapted for the other database.

In addition, abstracts from the following were searched:

- American Society of Hematology (ASH) (2000-2012)
- American Society of Clinical Oncology (ASCO) (2000-2011)
- International Myeloma Workshops (2000-2011)
- Cancer Guidelines.ca (http://www.cancerguidelines.ca/Guidelines/inventory/index.php)
- National Guideline Clearinghouse (http://www.guideline.gov/)
- Canadian Medical Association Infobase (https://www.cma.ca/En/Pages/clinical-practice-guidelines.aspx)
- Physicians Query Database (http://www.cancer.gov/cancertopics/pdq)
- ACP Journal Club (2000 to February 2012)

The files of Working Group members and the reference lists of included articles were also searched.

Study Selection Criteria

Articles were selected for inclusion in this systematic review if they were the following:

1. Studies of adult patients with multiple myeloma
2. Studies that tested the role of lenalidomide alone or in combination with other agents
3. Studies that reported results reported for any of the following outcomes:
    - Overall survival (OS)
    - Event-free survival (EFS)
    - Progression-free survival (PFS)
    - Time to progression (TTP)
    - Time to next treatment (TTNT)

- Response rate: Complete and partial response (CR and PR)
- Incidence of serious toxicity (i.e., grade 3 or 4 adverse events by the National Cancer Institute [NCI] toxicity criteria)

4. Studies that were systematic reviews or randomized controlled trials (phase II or phase III)
5. Non-randomized studies that were follow-ups or subanalyses of previous pivotal studies
6. Studies with a trial sample size ≥30
7. Studies published in English

Narrative reviews, phase I, and other comparative observational studies, case reports, non-comparative studies, studies with a population that did not include patients with multiple myeloma, studies looking at interventions that did not include lenalidomide, and publication types such as commentaries, editorials, and letters were excluded. Conference abstracts that were reports of non-final analyses were excluded following Program in Evidence-based Care (PEBC) policy. Cost-effectiveness and health-related quality of life were not considered outcomes of interest for this document.

Selection of Studies

The citations found by the electronic databases and the titles of the abstracts from conference proceedings were screened by the methodologist, who excluded those in which either population or intervention were not on target. The full text of the articles selected by the methodologist was retrieved, and the full set of selection criteria was applied independently by the methodologist and two clinician members of the Working Group. In cases of disagreement, consensus was achieved through discussion. The reasons for excluding articles were documented (see Appendix 3 in the original guideline document).

Number of Source Documents

After full text screening, 57 publications were included: two practice guidelines; three systematic reviews, of which one is in abstract form; 10 unique primary studies, of which five are full-text publications and five are conference abstracts. Forty-two publications were ancillary to the 10 unique primary studies and included secondary analyses or follow-up data from the main publications. Of these, 12 are full-text publications, and 30 are conference abstracts.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus (Committee)

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis of Randomized Controlled Trials

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Quality Assessment

To evaluate the quality of included evidence-based guidelines either the Appraisal of Guidelines Research and Evaluation, version II (AGREE II) tool was used by two independent methodologists or the AGREE II scores were taken from the Standards and Guidelines Evidence Inventory of Cancer Guidelines developed by the Canadian Partnership Against Cancer (CPAP), if available. Only clinical practice guidelines specifically describing the objective of the guideline and including a review of the evidence were evaluated using the AGREE II tool.

Systematic reviews and meta-analyses were assessed for quality using the Assessment of Multiple Systematic Reviews (AMSTAR) tool by two

independent methodologists.

The quality of the included primary studies has been evaluated by considering discrete parameters such as the required sample size and the actual sample size, allocation concealment, blinding, intention-to-treat analysis, ethical approval, losses to follow-up, and whether the randomization method was described, whether the study reported a final analysis, and whether the study was terminated early. For studies that were stopped early for benefit, additional parameters such as the planned accrual, the expected effect size, the number of events experienced and the stopping rule used, were considered.

Synthesizing the Evidence

Data were summarized in evidence tables and described in the text of the original guideline document. When clinically homogeneous results from two or more trials were available, the data were pooled using the Review Manager software (RevMan 5.1.2) provided by the Cochrane Collaboration. Since the hazard ratios (HRs), rather than the number of events at a certain time point, are the preferred statistic for pooling time-to-event outcomes, those were extracted directly from the most recently reported trial results. The variances of the HR estimates were calculated from the reported confidence intervals (CI). A random-effects model was used for all pooling.

Statistical heterogeneity was calculated using the X^2 test for heterogeneity and the I^2 percentage. A probability level for the X^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% were considered indicative of statistical heterogeneity. Results are expressed as HRs with 95% CI. An HR <1.0 indicates that patients receiving lenalidomide alone or in combination with other agents had a higher probability of experiencing an event (e.g., surviving without progression of disease); conversely, an HR >1.0 suggests that patients receiving lenalidomide alone or in combination with other agents experienced a lower probability of an event.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The evidence-based series (EBS) guidelines developed by the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO), use the methods of the Practice Guidelines Development Cycle. For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by two members of the Lenalidomide in Multiple Myeloma Working Group of the PEBC Hematology Disease Site Group (DSG) and by one methodologist.

The systematic review is a convenient and up-to-date source of the best available evidence on lenalidomide for multiple myeloma. The body of evidence in this review is primarily comprised of randomized controlled trial (RCT) data. That evidence forms the basis of the recommendations developed by the Hematology DSG.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Published cost analyses were reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Report Approval Panel Review and Approval

Prior to the submission of this evidence-based series (EBS) draft report for external review, the report was reviewed and approved by the Program in Evidence-based Care Report Approval Panel (PEBC RAP), which consists of three members, including an oncologist, with expertise in clinical and methodology issues.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC Report Approval Panel, the Hematology Disease Site Group (DSG) circulated Sections 1 and 2 to external review participants for review and feedback. Box 1 in the original guideline document summarizes the draft recommendations and supporting evidence developed by the Hematology DSG.

Methods

Targeted Peer Review

During the guideline development process, eight targeted peer reviewers from Ontario considered to be clinical and/or methodological experts on the topic were identified by the working group. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Seven reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on February 17, 2012. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The Hematology DSG reviewed the results of the survey.

Professional Consultation

Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. All hematologists, internists, medical oncologists, oncology nurses, and oncology pharmacists in the PEBC database were contacted by email to inform them of the survey. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on February 17, 2012. The consultation period ended on April 2, 2012. The Hematology DSG reviewed the results of the survey.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are supported by practice guidelines, systematic reviews, primary studies, and a meta-analyses when pooling of data was permitted.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Previously Untreated Symptomatic Multiple Myeloma

One study showed an improved, median one-year, progression-free survival (PFS) (78% versus [vs.] 52%; p=0.002), and improved overall response (OR) (77% vs. 48%; p<0.0001) in patients treated with lenalidomide plus dexamethasone versus patients treated with placebo and dexamethasone. Another study demonstrated a longer median PFS for lenalidomide in combination with low-dose dexamethasone versus

lenalidomide plus high-dose dexamethasone (25.3 vs. 19.1 months; p=0.026), with an improved safety profile (grade ≥3 adverse events: p=0.02 for neutropenia, p=0.0003 for deep-vein thrombosis [DVT], and p=0.04 for infections) in favour of the low-dose dexamethasone arm.

Relapsed or Refractory Multiple Myeloma

- Two seminal studies showed an improved time to progression (TTP) with lenalidomide plus dexamethasone as compared with dexamethasone plus placebo. The developers meta-analysis of these two studies showed that lenalidomide improved TTP (hazard ratio [HR], 0.35; 95% confidence interval [CI], 0.29 to 0.42; p<0.00001), overall survival (OS) (HR, 0.54; 95% CI, 0.36 to 0.80; p<0.002) and ORs (HR, 0.50; 95% CI, 0.44 to 0.58; p<0.00001) as compared to a non-lenalidomide regimen.
- Although high-dose dexamethasone dosing with lenalidomide was used in the two pivotal randomized controlled trials (RCTs) of relapsed/refractory myeloma, low-dose weekly dexamethasone with lenalidomide appears less toxic when used in the first-line setting. From a safety perspective, the Hematology Disease Site Group (DSG) considers low-dose dexamethasone a reasonable option for use in the relapsed/refractory setting. Once again, select subgroups with acute myeloma complications may still benefit from the greater response rates achievable with high-dose dexamethasone.

Subgroups of Patients Most Likely to Benefit From Treatment With Lenalidomide

The subgroup analyses of data are derived primarily from the Rajkumar study in the first-line setting and from pooled data from the Weber and Dimopoulos randomized studies in the relapsed/refractory setting. These data have been integrated with the clinical expertise of the Hematology DSG to provide support for these recommendations:

- There is limited evidence available at this time to recommend lenalidomide in specific subgroups of previously untreated patients. When lenalidomide is combined with dexamethasone, the use of low-dose dexamethasone may be preferable in both older and younger patients. Two subgroup analyses evaluating age of patients participating in the Rajkumar study reported improved overall survival in all age groups when treated with low-dose versus high-dose dexamethasone.
- A subgroup analysis showed that partial cross-resistance between thalidomide and lenalidomide may exist, but prior thalidomide exposure should not absolutely contraindicate the use of lenalidomide in the relapsed/refractory setting. The recommendation for patients who have had a prior autologous stem cell transplant (ASCT) is based on study stratification results and a separate pooled subgroup analysis.
- Lenalidomide and dexamethasone were found to be consistently superior to dexamethasone alone in subgroup analyses by several authors, and this recommendation is supported by the clinical expertise of the Hematology DSG.
- One subgroup analysis of patients remaining on lenalidomide beyond 12 months, report that those requiring dose reductions were able to stay on the study longer, tolerated therapy as well as those not requiring dose reductions, and achieved longer PFS.
- Two subgroup analyses suggests that continued therapy after achieving a partial remission (PR) was beneficial, possibly by leading to higher quality of response that in turn prolongs survival.
- A subgroup analysis identified that dose reductions of dexamethasone were associated with improved survival outcomes.

Lenalidomide Maintenance or Consolidation

- The search identified three companion abstract publications relevant to this question of maintenance after transplant that reported a significant improvement in complete response (p<0.01) and PFS (p<0.0001) with maintenance versus no maintenance. In addition, an ongoing randomized study presented in preliminary form strongly supports the benefit of post-transplant maintenance with an OS advantage over no maintenance. The median TTP was 43.6 versus 21.5 months; PFS was also favourable for the lenalidomide group (HR, 0.43; one-sided unadjusted p<0.0001). These combined data provide emerging support for the use of lenalidomide maintenance post-transplant, which the Hematology DSG, therefore, considers a reasonable post-transplant option.

Management of Toxicity

- In a published substudy of previously untreated patients participating in a lenalidomide-based study who were randomized to either aspirin (ASA) 100 mg daily or enoxaparin 40 mg/day subcutaneously for venous thromboembolism (VTE) prophylaxis. Equally low rates of VTE with no major hemorrhagic complications in either arm were reported, and therefore, the Hematology DSG recommends either option as reasonable. Given the favourable safety profile of both ASA and enoxaparin in prophylactic dosing, the generalization of these recommendations to the relapsed/refractory setting is not unreasonable until randomized data in this setting becomes available.
- A subgroup analysis of data pooled from the Weber and Dimopoulos trials suggested that, by allowing patients to tolerate therapy longer, dose reductions may be beneficial in prolonging PFS. In addition, the Weber and Dimopoulos RCTs routinely used granulocyte colony-stimulating factor (GCSF) support with full-dose lenalidomide as the initial dose-modification step for severe neutropenia, an approach that may also be appropriate. Based on the clinical expertise of the Hematology DSG, these data led to the recommendations for dose reductions in those patients with responsive disease and consideration for GCSF if full-dose lenalidomide for efficacy is required.

Potential Harms

Lenalidomide-induced toxicities include venous thromboembolism (VTE), cytopenias (including neutropenia, anemia, and thrombocytopenia), and second primary malignancies (SPM).

Qualifying Statements

Qualifying Statements

- The Zonder and Rajkumar studies have limitations: both studies were stopped early due to benefit, and the Rajkumar study used the overall response (OR) rate as the primary outcome. The Zonder study was sponsored by the pharmaceutical company producing the drug, and the Rajkumar et al study was sponsored by a government body. In the Rajkumar study, the improved safety profile and lower rate of early deaths associated with low-dose dexamethasone has led to widespread adoption of this approach, and from a safety perspective, the Hematology Disease Site Group (DSG) endorses this low-dose dexamethasone approach. It should be noted, however, that high-dose dexamethasone, though more toxic, was associated with higher response rates than was low-dose dexamethasone. Therefore, select patient populations such as those with acute renal dysfunction, hypercalcemia, or hyperviscosity syndrome may still benefit from the robust efficacy of high-dose dexamethasone.
- Two seminal studies were stopped at the first pre-planned interim analysis for benefit and were funded by the drug's manufacturer. However, the studies enrolled more than 300 patients before stopping and had a large number of events. The recommendation to use low-dose dexamethasone with lenalidomide in the relapsed/refractory setting is generalized from the Rajkumar study in newly diagnosed disease and is based primarily on improved safety. There are no comparative studies directly evaluating low-dose dexamethasone dosing in the relapsed/refractory setting.
- All the subgroup analyses upon which these recommendations or guidelines are based are retrospective, post hoc analyses. In isolation, they represent a weak evidence base and, therefore, have been integrated with the expert opinion and clinical experience of the Hematology DSG. The validation of these recommendations through further clinical investigation is required.
- One particular study has recently been published in full, though only preliminary abstract data were captured in this review. Another study was published only in abstract form at the time of our literature search, though it was a final analysis of a completed trial. It has since been published in full, but the complete publication was not analyzed for this review. This study was stopped early for benefit and was sponsored by the manufacturer of lenalidomide (see clinical trials.gov). One study was also captured in our search as an interim analysis, but has since undergone full publication. Even in interim analysis, an overall survival (OS) benefit favoring the lenalidomide maintenance arm was demonstrated. The Hematology DSG cautions that, although these data are compelling, further maturation of data is required before full recommendations for maintenance in post-transplant patients can be made.
- One superiority trial showed no difference between two drugs for the prevention of venous thromboembolism (VTE); untreated patients were 65 years of age or younger, the power of the study ranged from 47% to 80%, and for ethical reasons a placebo arm was not available. However, this was the first and only randomized controlled trial (RCT) studying VTE prophylaxis in patients with multiple myeloma treated with lenalidomide. Despite these study limitations, the Hematology DSG members believed that based on their clinical experience, these results could be generalized to other patient groups. If the 100-mg dose for aspirin (ASA) is not available, the Hematology DSG suggests that replacement with the 81-mg dose is reasonable.
- Erythropoietin-stimulating agents (ESA) may also be considered for the management of anemia related to lenalidomide therapy. In the absence of evidence for ESA use specific to lenalidomide therapy, published evidence-based guidelines for ESA use in cancer may be applied. In a subgroup analysis of the Weber and Dimopoulos studies that was published as a letter to the editor and excluded from our systematic review, the rates of venous thromboembolism were significantly higher with the concomitant use of ESA and lenalidomide versus lenalidomide without ESA. Therefore, the concomitant use of ESA with lenalidomide may potentiate the risk of thrombosis. As these observations mandate further validation, the Hematology DSG advises consideration of risks and benefits before initiating ESA with lenalidomide, followed by careful monitoring for VTE signs and symptoms. Transfusion of either red cells or platelets, in conjunction with lenalidomide dose reductions/interruptions, may be appropriate for severe or symptomatic anemia or thrombocytopenia.
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Chen C, Baldassarre F, Kanjeekal S, Herst J, Hicks L, Cheung M, Hematology Disease Site Group. Lenalidomide in multiple myeloma. Toronto (ON): Cancer Care Ontario (CCO); 2012 May 30. Various p. (Evidence-based series; no. 6-5). [86 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 May 30

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

Guideline Developer Comment

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Source(s) of Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Guideline Committee

Hematology Disease Site Group

Composition of Group That Authored the Guideline

For a current list of past and present members, please see the Cancer Care Ontario Web site .

Financial Disclosures/Conflicts of Interest

In accordance with the Program in Evidence-based Care (PEBC) Conflict of Interest (COI) Policy, the guideline authors, the members of the Hematology Disease Site Group (DSG), and internal and external reviewers were asked to disclose potential conflicts of interest.

Four guideline authors declared they had no conflicts. CC declared receiving trial support from Celgene, and MC declared being a site investigator on a lenalidomide clinical trial (MM-020) sponsored by Celgene.

Among the members of the Hematology DSG, RM declared that he received research funding from Celgene; AS declared that he was a principal investigator (PI) in a lenalidomide trial funded by Celgene; DR declared he received funding and was a PI in trials sponsored by Celgene, BMS, Janssen, Johnson & Johnson, Otsuka, Novartis, and Merk; the other members of the Hematology DSG declared that they had no conflicts of interest.

The internal reviewer and the three Report Approval Panel (RAP) members declared that they had no conflicts of interest.

Of the four targeted peer reviewers, one declared having received honoraria that exceeded CAD$5,000 in one year to act as a consultant for Celgene, Roche, and Janssen Ortho and also declared being the PI in a phase 3 lenalidomide trial.

Guideline Status

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site .

Availability of Companion Documents

The following is available:

- Program in evidence-based care handbook. Toronto (ON): Cancer Care Ontario (CCO); 2011. 15 p. Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on June 10, 2013. This summary was updated by ECRI Institute on March 10, 2014 following the U.S. Food and Drug Administration advisory on Low Molecular Weight Heparins.

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